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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,060	02/12/2002	David Mu	38002-0024	2406

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,060	MU ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9-12,14,22-24 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 9-12, 14, 22-24, and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Remarks and Amendment, filed April 16, 2004.

Claim 13 has been canceled. Claims 12 and 23 have been amended. Claims 4-8, 15-21, 25-32, and 36-38 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on October 27, 2003.

Claims 1-12 and 14-38 are pending in the instant application.

Claims 1-3, 9-12, 14, 22-24, and 33-35 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The specification is objected to because the specification at pages 11 and 67 contain embedded hyperlinks and/or other forms of browser-executable code that are impermissible and must be deleted. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Furthermore, if the application should issue and be placed on the Office web page, the URL may be interpreted as a valid HTML code and become a live web link, transferring a user to a commercial web site. Office policy does not permit the Office to link to any

commercial site because the Office exercises no control over the organization, views or accuracy of the information contained on these outside sites.

Claim Rejections - 35 USC § 112

In the previous Office Action filed on February 6, 2004, claims 1-3, 9-11, and 22-24 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is withdrawn** in view of the new 35 U.S.C. 112, first paragraph rejection for enablement as presented below:

Response to Arguments

Applicants arguments filed April 16, 2004 in response to the rejection under 35 U.S.C. 112, first paragraph against claims 1-3, 9-11, and 22-24 are moot in view of the Examiner's decision to withdrawn said rejection in view of the new 35 U.S.C. 112, first paragraph rejection for enablement as presented below:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 9-12, 14, 22-24, and 33-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

Claims 1-3 are drawn to a method for diagnosing a cancer in a mammal, comprising, detecting and measuring the hepsin gene copy number in a biological subject from a region of the mammal that is suspected to be precancerous or cancerous, thereby generating data for a test gene copy number; and comparing the test gene copy number to data for a control gene copy number, wherein an amplification of the gene in the biological subject relative to the control indicates the presence of a precancerous lesion or a cancer in the mammal. Claims 9-11 are drawn to a method for monitoring the efficacy of a therapeutic treatment regimen in a patient, comprising, measuring the hepsin gene copy number in a first sample of precancerous or cancer cells obtained from a patient, administering the treatment regimen to the patient, measuring the hepsin gene copy number in a second sample of precancerous or cancer cells from the patient at a time following administration of the treatment regions, and comparing the gene copy number in the first and the second samples, wherein data showing a decrease in the gene copy number levels in the second sample relative to the first sample indicates that the treatment regimen is effective in the patient. Claims 12 and 14 are drawn to a method for diagnosing a breast cancer or a lung cancer in a mammal, comprising, measuring the level of hepsin mRNA transcripts in a

biological subject from a region of the mammal that is suspected to be precancerous or cancerous, thereby generating data for a test level, and comparing the test level to data for a control level, wherein an elevated test level of the biological subject relative to the control level indicates the presence of a cancer or precancerous lesion in the mammal. Claims 22-24 are drawn to a method for monitoring the efficacy of a therapeutic treatment regimen in a patient comprising measuring at least one of hepsin mRNA or hepsin expression levels in a first sample of precancerous or cancer cell obtained from a patient, administering the treatment regimen to the patient, measuring at least one of hepsin mRNA or hepsin expression levels in a second sample of precancerous or cancer cells from the patient at the time following administration of the treatment regions and comparing at least one of hepsin mRNA or hepsin expression levels in the first and the second samples, wherein data showing a decrease in the levels in the second sample relative to the first sample indicates that the treatment regimen is effective in the patient. Claims 33-35 are drawn to a method for diagnosing a cancer in a mammal, comprising, detecting hepsin protein expression by contacting a biological subject from a region of the mammal that is suspected to be precancerous or cancerous with anti-hepsin antibody thereby generating data for a test level, and comparing the test level to data for a control level, wherein an elevated test level of the biological subject relative to the control level indicates the presence of a cancer or precancerous lesion in the mammal.

The instant specification teaches, by way of examples, 5 of 29 ovarian cancer cell lines tested exhibited at least 2.5 fold increase in hepsin DNA copies (17% frequency); 3 of 8 ovarian tumor cell lines tested exhibited at least 2.5 fold increase in hepsin DNA copies (38% frequency); and the hepsin gene was found amplified with a frequency of 3% and 6% in tested

lung and breast tumors, respectively (see pages 65 and 65, lines 26-31 and 1-13). Also, page 65, lines 28 and 29, indicates that 4 of 5 ovarian cancer cell lines tested exhibited hepsin overexpression in the range of 10 to 100 fold. Furthermore, in ovarian tumors, 25 of 29 tested exhibited at least 5 fold increase in hepsin mRNA expression compared to normal, while 5 of 9 ovarian tumor cell lines tested exhibited at least 5 fold increase in hepsin mRNA expression compared to normal. In prostate tumors, 8 metastatic prostate tumors overexrpessed hepsin mRNA, in the range of 7.7 to 89 fold in the tumor tissue (see page 66, lines 16-26). The Art teaches hepsin overexpression was above the mean normal level by + 2 SD (2+) or by + 4 SD (4+) (see Tanimoto et al. Cancer Research, 1997 Vol. 57:2884-2887, at Table 1). Magee et al. (Cancer Research, 2001 Vol. 61:5692-5696) teach prostate tumor samples tested exhibit a $\geq$3 fold increase in hepsin expression relative to control/benign samples (see Table 1). Stephan et al. (Journal of Urology, 2004 Vol. 171:187-191) teach in 48 patients, hepsin over expression was more than 10-fold in cancerous prostate tissue compared to normal prostate tissue (see Abstract).

The claims encompass a broad threshold of (1) amplification of the hepsin gene in the biological subject relative to the control (as recited in claims 1-3), (2) decreases in the hepsin gene copy number levels in the second sample relative to the first sample (as recited in claims 9-11), (3) elevation of test levels of the biological subject relative to the control levels (as recited in claims 12 and 14), (4) decreases in the levels in the second sample relative to the first sample (as recited in claims 22-24, and (5) elevation of test levels of the biological subject relative to the control levels (as recited in claims 33-35, where the specification and Art demonstrate that specific embodiments must be met to achieve successful and predictable results of the claimed methods.

Based on the guidance in the specification and what is taught in the Art, the skilled artisan would conclude that to practice the claimed methods, specific threshold embodiments must be met and achieved. These specific threshold embodiments are not required by the instant claims and one of ordinary skill in the art would need to undergo undue trial and error experimentation to determine what threshold parameters would need to be met before practice of the claimed methods can be successfully achieved. This undue experimentation would include the determination of specific threshold parameters, including percent folds of hepsin reduction, amplification, duplication, or overexpression, which would be significant to result in the diagnosis of cancer or efficacy of therapeutic treatment in a mammal. Given the art-recognized requirement for such parameters, this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods claimed, the nature of the invention, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary, one skilled in the art would not be able to practice the methods of claims 1-3, 9-12, 14, 22-24, and 33-35 without undue trial and error experimentation.

Claim Rejections - 35 USC § 102

In the previous Office Action filed on February 6, 2004, claims 12-14 were rejected under 35 U.S.C. 102(b) as being anticipated by Tanimoto et al. (Cancer Research, 1997 Vol. 57:2884-2887) [Applicants reference A63]. **This rejection is withdrawn** in view of Applicants Amendments to the claims, filed April 16, 2004, to recite a method for diagnosing a breast

cancer or a lung cancer in a mammal. It is noted that Tanimoto et al. disclose a method for detecting hepsin overexpression in ovarian cancer and not breast or lung cancer.

In the previous Office Action filed on February 6, 2004, claims 33-35 were rejected under 35 U.S.C. 102(b) as being anticipated by Zacharski et al. (Thromb Haemost, 1998 Vol. 79:876-877) [Applicants reference A72].

Zacharski et al. disclose immunohistochemical techniques using purified polyclonal monospecific anti-hepsin antibodies to study hepsin expression in renal cell carcinoma and normal renal tissues *in situ* (see page 876, second column, last paragraph and Figure 1). Zacharski et al. further disclose staining of normal tissue and other tumor types, including ovarian cancer, adenocarcinoma and squamous cell carcinoma of the lung (see page 877, first column). The data of Zacharski et al. is stored in the Thromb Haemost Journal in paper format.

This rejection is maintained for the reasons of record set forth in the previous Office Action filed February 6, 2003.

Response to Arguments

In response to this rejection, Applicants argue that Zacharski et al. used immunohistochemical techniques using purified polyclonal monospecific anti-hepsin antibodies to study hepsin expression. Applicants contend that Zacharski et al. do not disclose a method for diagnosing a cancer in mammal by detecting hepsin protein expression, nor does Zacharski et al. suggest that hepsin is amplified or overexpressed in tumor lines compared to normal cell.

Applicant's arguments have been fully considered, but are not found persuasive because Zacharski et al. disclose each and every method step recited in the instant claims. For example, Zacharski et al. disclose immunohistochemical techniques using purified polyclonal monospecific anti-hepsin antibodies to study hepsin expression in renal cell carcinoma and normal renal tissues *in situ* (see page 876, second column, last paragraph and Figure 1). Zacharski et al. further disclose staining of normal tissue and other tumor types, including ovarian cancer, adenocarcinoma and squamous cell carcinoma of the lung. Since Zacharski et al. disclose every method step recited in the instant claims, the experiments performed by Zacharski et al. would inherently comprise a method for diagnosing a cancer in a mammal, absent evidence to the contrary. While Zacharski et al. do not suggest that hepsin is amplified or overexpressed in tumor lines compared to normal cell, these parameters are not required by the instant claims. The claims do not recite that hepsin is amplified or overexpressed in tumor lines compared to normal cell. Therefore, Zacharski et al. anticipate claims 33-35 since every method step recited in the instant claim is disclosed and the experiments performed by Zacharski et al. would inherently comprise a method for diagnosing a cancer in a mammal, absent evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
June 22, 2004

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